

(19)



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(11)

**EP 1 031 347 B1**

(12)

**EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:  
17.04.2002 Bulletin 2002/16

(51) Int Cl.7: **A61K 9/127, A61K 38/19, A61K 39/39, A61K 38/28**

(21) Application number: 99101480.4

(22) Date of filing: 27.01.1999

**(54) Transnasal transport/immunisation with highly adaptable carriers**

Transnasaler Transport bzw. Impfung mit hochadaptierbaren Trägern

Transport/immunisation transnasale avec véhicules très adaptables

(84) Designated Contracting States:  
**AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE**  
Designated Extension States:  
**LT LV RO SI**

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(43) Date of publication of application:  
30.08.2000 Bulletin 2000/35

(56) References cited:  
**EP-A- 0 475 160 WO-A-90/09385**  
**WO-A-92/04009**

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- **DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US ALMEIDA A J ET AL: "Nasal delivery of vaccines." XP002107393 -& JOURNAL OF DRUG TARGETING, (1996) 3 (6) 455-67. REF: 125 JOURNAL CODE: B3S. ISSN: 1061-186X., XP002109107 Switzerland**
- **CEVC G: "Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery" CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS, vol. 13, no. 3-4, 1996, pages 257-388, XP002107366**

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delivery by noninvasive routes. *Crit-Rev-Ther-Drug-Carrier-Syst.* 1991; 8: 331-94

Westenberg-HG; Hijman-R; Wiegant-VM; Laczi-F; Van-Ree-JM Pharmacokinetics of DGAVP in plasma following intranasal and oral administration to healthy subjects. *Peptides.* 1994; 15: 1101-4

van-der-Wiel-HE; Lips-P; Nauta-J; Kwakkel-G; Hazenberg-G; Netelenbos-JC; van-der-Vijgh-WJ Intranasal calcitonin suppresses increased bone resorption during short-term immobilization: a double-blind study of the effects of intranasal calcitonin on biochemical parameters of bone turnover. *J-Bone-Miner-Res.* 1993; 8: 1459-65

## Claims

1. Use of a penetrant, suspended or dispersed in a solvent, in the form of a minute fluid droplet surrounded by a membrane-like coating of one or several layers of at least two different substances or two different forms of a substance with the tendency to aggregate, said substances or forms of a substance differing by at least the factor of 10 in the solubility in a preferably aqueous, liquid medium, such that the average diameter of homo-aggregates of the more soluble substance or form of the substance or the average diameter of the hetero-aggregates consisting of both said substances or forms of said substance is smaller than the average diameter of homo-aggregates of the less soluble substance or forms of the substance and/or wherein the more soluble component tends to solubilise the penetrating droplet and wherein the content of such component amounts to up to 99 mol-% of the concentration required to solubilise the droplet or else corresponds to up to 99 mol-% of the saturating concentration in the un-solubilised droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounded by the membrane-like coating is at least 5x lower, more preferably is at least 10x lower and ideally is more than 10x lower than that of the red blood cells or of the phospholipid bilayers with fluid aliphatic chains as a carrier for the preparation of a pharmaceutical, preferably a vaccine composition, for transnasal administration.
2. Use of a penetrant, suspended or dispersed in a solvent, in the form of a minute fluid droplet surrounded by a membrane-like coating of one or several layers of at least two different substances or two different forms of a substance with the tendency to aggregate, said substances or forms of a substance differing by at least the factor of 10 in the solubility in a preferably aqueous, liquid medium, such that the average diameter of homo-aggregates of the more

soluble substance or form of the substance or the average diameter of the hetero-aggregates consisting of both said substances or forms of said substance is smaller than the average diameter of homo-aggregates of the less soluble substance or form of the substance and/or wherein the more soluble component tends to solubilise the penetrating droplet and wherein the content of such component amounts to up to 99 mol-% of the concentration required to solubilise the droplet or else corresponds to up to 99 mol-% of the saturating concentration in the un-solubilised droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounded by the membrane-like coating is at least 5x lower, more preferably is at least 10x lower and ideally is more than 10x lower than that of the red blood cells or of the phospholipid bilayers with fluid aliphatic chains, said penetrant being used in combination with a pharmaceutically active ingredient or an allergen or an antigen for the preparation of a transnasally administerable pharmaceutical composition for the treatment of infective diseases, endocrine disorders, preferably hypopituitarism, diabetes, hyperthyroidism, thyroiditis, most preferably Hashimoto's thyroiditis, subacute thyroiditis; adrenal disorders, preferably Addison's disease, secondary adrenal insufficiency, Cushing's syndrome; gastrointestinal disorders, preferably Crohn's disease, colitis; hemorrhagic diseases, preferably hemophilia, leukopenia, hypereosinophilic syndrome; musculoskeletal and connective tissue disorders, preferably rheumatoid arthritis, Sjögren's syndrome, Bechet's syndrome, lupus, scleroderma, polymyositis/dermatomyositis, polymyalgia rheumatica and temporal arthritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue disorder, ankylosing spondylitis, psoriatic arthritis; osteoarthritis, Paget's disease, sciatica, bursitis, tendonitis and tenosynovitis, epicondylitis, fibromyalgia, eosinophilic fasciitis; neurological disorders, preferably pain, singultus, vertigo, seizure disorders, sleep disorders, transient ischemic attacks, spinal cord injury, demyelinating diseases, nerve root disorders, myasthenia gravis; oncological disorders; psychiatric disorders, preferably drug dependence, neuroses, mood disorders, schizophrenic disorders, delusional disorders; and/or for use in the field of gynecology, preferably for the treatment of dysmenorrhea, menopause, chronic anovulation, premature ovarian failure, endometriosis, infertility; and/or for use in the field of immunology, preferably transplant rejection, hyposensitization, allergen immunotherapy or prophylactic vaccination.

3. The use of claim 2 wherein the pharmaceutically active ingredient is an adrenocorticostaticum, an adrenolyticum, an androgen or antiandrogen, an

- antiparasiticum, an anabolicum, an anaestheticum or analgesicum, an analepticum, an antiallergicum, antiarrhythmicum, antiarteroscleroticum, antiasthmaticum and/or bronchospasmolyticum, an antibioticum, antidrepressivum and/or antipsychoticum, 5 an antidiabeticum, an antidot, an antiemeticum, antiepilepticum, antifibrinolyticum, anticonvulsivum or anticholinergicum, an enzyme, a coenzyme or the corresponding enzyme inhibitor, an antihistaminicum or antihypertonicum, an antihypotonicum, anticoagulant, antimycoticum, antimyasthenicum, an agent against Morbus Alzheimer or Morbus Parkinson, an antiphlogisticum, antipyreticum, antirheumaticum, antisepticum, a respiratory analepticum or a respiratory stimulant, a broncholyticum, cardiotonicum, chemotherapeuticum, a coronary dilatator, a cytostaticum, a diureticum, a ganglium-blocker, a glucocorticoid, an anti-flu agent, a haemostaticum, hypnoticum, an immunoglobuline or its fragment or any other immunologically active substance, such as an immunomodulator, a bioactive carbohydrate (derivative), a contraceptive, an antimigraine agent, a corticosteroid, a muscle relaxant, a narcoticum, a neurotherapeuticum, a (poly)nucleotide, a neurolepticum, a neurotransmitter, a (poly) peptide (derivative), an opiate, an ophthalmicum, (para)-sympaticomimeticum or (para)sympathicoliticum, a protein(derivative), a psoriasis/neurodermitis drug, a mydriaticum, a psychostimulant, rhinologicum, a sleep-inducing agent, a sedating agent, a spasmolyticum, tuberculostaticum, urologicum, a vasoconstrictor or vasodilatator, a virustaticum, a wound-healing substance, an inhibitor (antagonist) or a promoter (agonist) of the activity of any of above mentioned agents or any combination of said active substances.
4. The use of claim 2 wherein the antigen is derived from a pathogen.
5. The use of claim 2 wherein said pathogen belongs to extracellular bacteria, including pus-forming cocci, such as *Staphylococcus* and *Streptococcus*, gram-negative bacteria, such as *Meningococcus* and *Gonococcus* species, species of *Neisseria*, gram negative bacteria, including enteric organisms such as *E. coli*, *Salmonella*, *Shigella*, *Pseudomonas*, *Diphtheria*, *Bordetella Pertussis*, and gram-positive bacteria (e.g. *Bacillus pestis*, *BCG*), particularly anaerobes, such as the *Clostridium* species, bacteria and viruses, which survive and replicate within host cells, comprising mycobacteria (e.g. *M. tuberculosis*) and *Listeria monocytogenes*, retro- and adenoviruses, including hepatitis virus, (human) immunodeficiency virus, herpes viruses, small-pox (chicken-pox), influenza, measles, mumps and polio viruses, cytomegalovirus, rhinovirus, etc., and fungi prospering inside host cells, a parasite including animal parasites, such as protozoa and helminths, and ectoparasites, such as ticks and mites, or *Brucella* species, including the causative agent for cholera, *Haemophilus* species, as well as pathogens triggering paratyphoid, plague, rabies, tetanus and rubella diseases or to eukaryotic cells or their parts that cause various neoplasiae, auto-immune diseases and other pathological states of the animal or human body which do not necessarily result from microbial infections.
6. The use of claim 2 wherein the antigen is used in a purified or even better in a pure form.
7. The use of claim 2 wherein the antigen is the antigenic determinant of hepatitis virus, (human) immunodeficiency virus, herpes viruses, small-pox (chicken-pox), influenza, measles, mumps and polio viruses, cytomegalovirus, rhinovirus, etc., and fungi prospering inside host cells, a parasite including animal parasites, such as protozoa and helminths, and ectoparasites, such as ticks and mites, or *Brucella* species, including the causative agent for cholera, *Haemophilus* species, as well as pathogens triggering paratyphoid, plague, rabies, tetanus and rubella diseases or else eukaryotic cells or their parts that cause various neoplasiae, auto-immune diseases and other pathological states of the animal or human body, which do not necessarily result from microbial infections.
8. The use of claim 2 wherein the allergen is of xenogenic or endogenic origin, derived from a microorganism, an animal or a plant, or belonging to the group of man made and/or irritating inorganic substances, or to such parts or components of the human body which were incorrectly processed by or exposed to the body immune system.
9. The use of claim 2 wherein the allergen belongs to the class of the inhalation allergens, including but not limited to various pollen, spores, bits of animal hair, skin, feather, natural and synthetic textiles, wheat, (house) dust, including mite; furthermore, food and drug allergens; contact allergens; injection, invasion or depot allergens, such as various (gastrointestine-resident) worms, echinococci, trichines, etc., a part of implantation material.
10. The use of any one of claims 1 and 2 and 3 to 9 additionally comprising a compound which releases or induces cytokine or anti-cytokine activity or exerts such an activity itself.
11. The use of claim 10 wherein the compound exerting cytokine activity is IL-4, IL-2, TGF, IL-6, TNF, IL-1 $\alpha$  and IL-1 $\beta$ , a type I interferon, preferably IFN-alpha or IFN- $\beta$ , IL-12, IFN- $\gamma$ , TNF- $\beta$ , IL-5 or IL-10.

12. The use of claim 10 wherein said compound with anti-cytokine activity is an anti-cytokine antibody or the corresponding active fragment, a derivative, or an analogue thereof.
13. The use of claim 12 wherein the compound displaying or inducing cytokine or anti-cytokine activity and the pharmaceutically active ingredient or antigen or allergen are associated with the penetrant.
14. The use of any one of claims 1 to 13 wherein the less soluble self-aggregating molecule is a lipid, preferably a polar lipid, and the more soluble component is a surfactant or some more soluble form of the polar/basic lipid.
15. The use of any one of claims 1 to 14 wherein the more soluble component is an agent to be transported across the barrier, said agent having a tendency to form common large structures with the less soluble component(s) of the penetrant, typically in the form of a physical or a chemical complex.
16. The use of any one of claims 1 to 15 wherein the more soluble component tends to solubilise the penetrating droplet and is present in concentration not exceeding 99 mol% of the concentration required to disintegrate the droplet or, alternatively, not exceeding 99 mol% of the saturating concentration in the unsolubilised droplet, whichever is higher, values below 50 % of the former relative concentration being particularly useful, with values below 40 rel-% or even around and below 30 rel-% being even more advantageous, whereas in the case of droplets which cannot be solubilised by the more soluble component relative concentrations which exceed the above mentioned relative concentrations by the factor of up to 2 are most preferred.
17. The use of any one of claims 1 to 16 wherein the less soluble penetrant component is a polar lipid and the more soluble component is a surfactant or a surfactant-like molecule or else such form of a lipid, preferably a polar lipid which is sufficiently soluble for the purpose of this invention.
18. The use of any one of claims 1 to 17 wherein the average penetrant diameter is between 25 nm and 500 nm, preferably between 30 nm and 250 nm, even more preferably between 35 nm and 200 nm and particularly preferably between 40 nm and 150 nm.
19. The use of any one of claims 1 to 18 wherein the penetrant concentration in the formulation for the use in human or animal nose is 0.001 to 20 weight-% of total dry mass in the formulation, in particular between 0.01 w-% and 15 w-%, more preferably between 0.1 w-% and 12.5 w-% and most preferred between 0.5 w-% and 10 w-%.
20. The use of any one of claims 1 to 19 wherein the supporting medium, e.g. a buffer, is selected to be a biocompatible solution with an osmotic activity similar to that of a monovalent electrolyte with concentration in the range between 1 mM and 500 mM, more preferably between 10 mM and 400 mM, even more preferably between 50 mM and 300 mM, and most preferably between 100 mM and 200 mM or else such solution that affords practically sufficient penetrant stability combined with practically sufficient transport rate across the barrier.
21. The use of any one of claims 1 to 20 wherein the relative drug or agent concentration is between 0.001 and 40 weight-% of total penetrant mass, in particular between 0.01 w-% and 30 w-%, even better between 0.1 w-% and 25 w-% and most preferably between 0.5 w-% and 15 w-%.
22. The use of any one of claims 1 to 21 wherein the medium supporting the drugs and carriers is a biocompatible buffer with pH value between 4 and 10, more frequently between 5 and 9 and most often between 6 and 8.
23. The use of any one of claims 1 to 22 wherein the additives are included in the preparation to reduce the system sensitivity to chemical, biological or ambient stress, including anti-oxidants, antagonists of undesired enzyme action, cryo-preservatives, microbicides, etc., or else modulators of physically important system properties, such as formulation viscosity, etc..
24. The use of any one of claims 1 to 23 wherein the relative drug or agent dose to be administered non-invasively through the nose by means of highly adaptable carriers is chosen to be between 0.1x and 500x, more often between 0.5x and 250x, and even more preferably between 1x and 100x different from the corresponding drug or agent dose that would have to be injected to achieve the desired biological effects.
25. The use of any one of claims 1 to 24 wherein the applied penetrant dose is between 0.01 mg and 15 mg per nostril, even more often is in the range 0.1 mg and 10 mg per nostril, and preferably is between 0.5 mg and 5 mg per nostril.
26. The use of any one of claims 1 to 25 wherein the efficiency of administration and the biological effects of the agent or drug chosen are controlled by using different application volumes.

27. The use of any one of claims 1 to 26 wherein said formulation is administered using a metered delivery device.
28. The use of any one of claims 1 to 27 wherein different application volumes are selected to control the efficiency of administration and the biological effects of the chosen agent or drug.
29. The use of any one of claims 1 to 28 wherein the penetrants in suspension are loaded with the drugs or agents within 24 hours prior to the formulation administration, preferably 360 min, more preferably 60 min and even more preferably 30 min before the resulting formulation administration in the nose.
30. The use of any one of claims 1 to 29 wherein the delivery device is loaded at the treatment site.
31. The use of any one of claims 1 to 30 wherein the device is loaded separately with penetrants and the molecules, particularly biological agents, to be associated therewith.
32. The use of any one of claims 1 to 31 wherein the pharmaceutically active ingredient is for administration to the nervous system.
33. The use of claim 32 wherein the nervous system is the brain.
34. The use of any one of claims 1 to 33 wherein said pharmaceutical composition is a vaccine.
35. The use of claim 34 wherein the vaccine further comprises a pathogen extract or a compound from a pathogen or a fragment or a derivative thereof.
36. The use of claim 35 wherein said pathogen extract or compound is selected from hepatitis virus, (human) immunodeficiency virus, herpes viruses, small-pox (chicken-pox), influenza, measles, mumps or polio viruses, cytomegalovirus, rhinovirus, etc., or fungi prospering inside host cells, a parasite including animal parasites, such as protozoa and helminths, and ectoparasites, such as ticks and mites, or *Brucella* species, including the causative agent for cholera, *Haemophilus* species, as well as pathogens triggering paratyphoid, plague, rabies, tetanus or rubella diseases.
37. The use of any one of claims 34 to 36 wherein said vaccine further comprises an adjuvant.
38. The use of claim 37 wherein said adjuvant is lipopolysaccharide, such as lipid A or a derivative or modification thereof, such as monophosphoryl lipid A, or its analogue, such as a fatty derivative of saccharose, cord-factor (trehalose-dimycolate), muramyl dipeptide, or another (poly)saccharide or (poly)peptide identical to or resembling an immunologically active part of a membrane of a microorganism; an extract of a microorganism, including bacterial exo- and endotoxins, preferably cholera toxin or the heat labile toxin of *E. coli*, an A-chain derivative, a component with an ADP-ribosylating activity, a peptidoglycane, a clostridial toxin, an LT halotoxin, purified protein derivative of *M. tuberculosis*, LT-R192G, Fibronectin-binding protein I of *Streptococcus pyrogenes*, or outer membrane protein of group B *Neisseria meningitidis* (GBOMP).
39. The use of any one of claims 34 to 38 wherein said vaccine comprises a blend of MPL and IL-12 or GM-CSF and IL-4.
40. The use of any one of claims 34 to 39 wherein in said vaccine the relative immunogen/antigen dose to be administered non-invasively through the nose by means of highly adaptable carriers is chosen to be between 0.01x and 100x, more often between 0.05x and 75x, and even more preferably between 0.1x and 50x different from the corresponding immunogen/antigen dose that would have to be injected to achieve the desired biological effect.
41. The use according to any one of claims 37 to 40 wherein in said vaccine the concentration of the transnasally administered adjuvant is between 10x lower and up to 1000x higher than that used with the corresponding subcutaneously injected formulations employing similar antigen, the transnasally administered immunoadjuvant concentration more often differing from the injected immunoadjuvant concentration by the factor between 0.5 and 100, or better, by the factor between 1 and 50, and best between 2 and 25.

#### Patentansprüche

1. Verwendung eines Durchdringungsmittels, suspendiert oder dispergiert in einem Lösungsmittel, in der Form eines winzigen Flüssigkeitstropfens, der von einer membranähnlichen Hülle aus einer oder mehreren Schichten von mindestens zwei verschiedenen Stoffen oder zwei verschiedenen Formen eines Stoffes, mit der Tendenz zu aggregieren, umgeben ist, wobei die Stoffe oder Formen eines Stoffes sich mindestens um den Faktor 10 in der Löslichkeit in einem vorzugsweise wässrigen, flüssigen Medium unterscheiden, so dass der mittlere Durchmesser von Homoaggregaten des löslicheren Stoffes oder Form des Stoffes oder der mittlere Durchmesser der Heteroaggregate bestehend aus beiden Stoffen oder Formen des Stoffes kleiner ist als der mittlere